

1 WHAT IS CLAIMED IS:

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A ~~2~~ A pharmaceutical composition comprising a matrix capable of delivering at least one
3 therapeutic agent to a bodily compartment under controlled release conditions, said
4 matrix comprising a homogeneous mixture of aqueous phase and at least one other phase,
5 at least one therapeutic agent present in at least one of said phases, and at least one cross-
6 linked polymer physically entrapping said at least one therapeutic agent.

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8 2. The pharmaceutical composition of claim 1 wherein said at least one other phase is a
solid phase, an oil phase, or a combination thereof.

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11 3. The pharmaceutical composition of claim 2 wherein said oil phase and said aqueous
12 phase are in the form of an emulsion.

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14 4. The pharmaceutical composition of claim 1 wherein said polymer comprises a backbone
15 selected from the group consisting of a poly(alkylene oxide), carboxymethylcellulose,
16 dextran, modified dextran, polyvinyl alcohol, N-(2-hydroxypropyl)methacrylamide,
17 polyvinyl pyrrolidone, poly-1,3-dioxolane, poly-1,3,6-trioxane, polypropylene oxide, a
18 copolymer of ethylene and maleic anhydride, a polylactide/polyglycolide copolymer, a
19 polyaminoacid, a copolymer of poly(ethylene glycol) and an amino acid, and a
20 polypropylene oxide/ethylene oxide copolymer.

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22 5. The pharmaceutical composition of claim 1 wherein said polymer comprises at least two
23 functional or reactive groups.

1 6. The pharmaceutical composition of claim 5 wherein said functional groups are amino,
2 carboxyl, thiol, hydroxy, or any combination thereof.

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4 7. The pharmaceutical composition of claim 6 wherein said polymer is an poly(alkylene
5 oxide) derivative.

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7 8. The pharmaceutical composition of claim 7 wherein said poly(alkylene oxide) derivative
8 is selected from the group consisting of α,ω -dihydroxy-poly(ethylene glycol) and
 α,ω -diamino-poly(ethylene glycol).

9 9. The pharmaceutical composition of claim 6 wherein said functional groups are thiol
groups.

10 10. The pharmaceutical composition of claim 9 wherein said polymer is prepared from
11 α,ω -diamino-poly(ethylene glycol) and thiomalic acid; α,ω -dihydroxy-poly(ethylene
12 glycol) and thiomalic acid; or α,ω -dicarboxy-PEG subunits and lysine, wherein free
13 carboxy groups on said lysine are derivatized to provide thiol groups.

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15 11. The pharmaceutical composition of claim 9 wherein said thiol groups on said polymer are
16 cross-linked by thioether or disulfide bonds.

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19 12. The pharmaceutical composition of claim 9 wherein said thiol groups on said polymer are
20 sterically hindered.

1 13. The pharmaceutical composition of claim 1 wherein said at least one therapeutic agent is
2 selected from the group consisting of a small-molecule drug, a protein, a nucleic acid and
3 a polysaccharide.

4
5 14. The pharmaceutical composition of claim 13 wherein said small-molecule drug is
6 selected from the group consisting of an anticancer drug, a cardiovascular drug, an
7 antibiotic, an antifungal, an antiviral drug, an AIDS drug, an HIV-1 protease inhibitor, a
8 reverse transcriptase inhibitor, an antinociceptive drug, a hormone, a vitamin, an
9 anti-inflammatory drug, an angiogenesis drug, and an anti-angiogenesis drug.

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11 15. The pharmaceutical composition of claim 1 wherein said matrix has at least one
12 controlled release in-vivo kinetic profile selected from the group consisting of zero order,
13 pseudo zero order, and first order.

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15 16. The pharmaceutical composition of claim 1 wherein said controlled release conditions is a
16 constant rate of release.

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18 17. The pharmaceutical composition of claim 1 wherein said matrix further comprises an
19 excipient.

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21 18. The pharmaceutical composition of claim 17 wherein said excipient is selected from the
22 group consisting of a monovalent metal ion, a polyvalent metal ion, an anionic polymer, a
23 cationic polymer, a nonionic polymer, a surfactant, and a protein.

1 19. A method for preparing the pharmaceutical composition of claim 1 comprising the steps
of

- 3 i) preparing a mixture comprising at least one therapeutic agent and at least
4 two phases one of which is an aqueous phase, said aqueous phase
5 comprising a polymer having at least two functional groups thereon;
6 ii) cross-linking said polymer under conditions to form a cross-linked matrix
7 having said therapeutic agent entrapped therein.

8 20. The method of claim 19 wherein said functional groups are thiol groups.

9 21. The method of claim 20 wherein said conditions that cause cross-linking of said thiol
10 groups comprises reaction in the presence of an oxidizing agent or reaction with a
11 cross-linking agent.

12 22. The method of claim 21 wherein said oxidizing agent is selected from the group
13 consisting of molecular oxygen, hydrogen peroxide, dimethylsulfoxide, and molecular
14 iodine.

15 23. The method of claim 21 wherein said cross-linking agent is a bifunctional disulfide-
16 forming or thioether-forming cross-linking agent.

17 24. The method of claim 23 wherein said cross-linking agent is selected from the group
18 consisting of 1,4-di-[3',2'-pyridyldithio(propionamido)butane];
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1 α,ω -di-O-pyridyldisulfidyl-poly(ethylene glycol); α,ω -divinylsulfone-poly(ethylene
2 glycol); α,ω -diiodoacetamide-poly(ethylene glycol) and 1,11-bis-maleimidotetraethylene
3 glycol.
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5 25. A method for delivering at least one therapeutic agent to a bodily compartment to an
6 animal under controlled release conditions comprising providing in said bodily
7 compartment a pharmaceutical composition set forth in claim 1.
8

9 26. The method of claim 25 wherein said bodily compartment is subcutaneous, oral,
10 intravenous, intraperitoneal, intradermal, subdermal, intratumor, intraocular, intravisceral,
11 intraglandular, intravaginal, intrasinus, intraventricular, intrathecal, intramuscular, and
12 intrarectal.
13

14 27. The method of claim 26 wherein said composition is provided to said bodily
15 compartment by a route selected from the group consisting of subcutaneous, oral,
16 intravenous, intraperitoneal, intradermal, subdermal, intratumor, intraocular, intravisceral,
17 intraglandular, intravaginal, intrasinus, intraventricular, intrathecal, intramuscular, and
18 intrarectal.
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20 ~~The method of claim 25 wherein said controlled release conditions occur as a~~
21 ~~consequence of diffusion from said matrix or biodegradation of said matrix by an in-vivo~~
22 ~~degradation pathway selected from the group consisting of reducing agents, reductases,~~

1 ~~A3~~ S-transferases, peptidases, proteases, non-enzymatic hydrolysis, esterases and
2 ~~cat~~ thioesterases

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4 29. The method of claim 25 wherein said providing in said bodily compartment is carried out
5 by forming said matrix immediately prior to or during administration of said matrix to
6 said animal.

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8 30. The method of claim 29 wherein said pharmaceutical composition is capable of being
9 injected as a liquid or semisolid gel through a small gauge needle, begins cross-linking
10 and entrapping said therapeutic agent during injection, and completes cross-linking and
11 physically entrapping said therapeutic agent within several minutes of being injected.

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13 31. The method of claim 25 wherein said controlled release conditions comprise a time
14 course of release of five or more days.

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16 32. The method of claim 31 wherein said time course of release is twenty or more days.

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18 33. The method of claim 25 wherein said releasing comprises a controlled release profile
19 comprising an optional bolus release profile followed by a release profile selected from
20 the group consisting of zero order, pseudo zero order, and first order.

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22 34. A method of administering a controlled release therapeutic agent to a mammal, said
23 method comprising: preparing a solution comprising a hydrogel forming polymer having

1 two or more thiol groups and a plurality of phases, one of which is an aqueous phase, a
2 cross-linking agent comprising two or more thiol-reactive groups, and a therapeutically
3 effective amount of drug; and injecting said mammal with said solution whereby a
4 hydrogel drug depot is formed at the site of injection having said drug temporarily
5 entrapped therein.

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7 35. The method of claim 34, wherein said controlled release therapeutic agent has a kinetic
8 profile comprising an optional initial bolus release profile followed by a release profile
selected from the group consisting of zero order, pseudo zero order, and first order.

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10 36. The method of claim 34 wherein said thiol-reactive cross-linking agent is an oxidizing
11 agent; 1,4-di-[3',2'-pyridyldithio(propionamido)butane];
12 α,ω -di-O-pyridyldisulfidyl-poly(ethylene glycol); α,ω -divinylsulfone-poly(ethylene
13 glycol); α,ω -diiodoacetamide-poly(ethylene glycol) or 1,11-bis-maleimidotetraethylene
14 glycol.

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17 ~~A hydrogel composition comprising a homogeneous mixture of aqueous phase and at~~
18 ~~least one other phase, and at least one cross-linked polymer in one of said phases.~~
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